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β -Adrenoceptor-mediated thermogenesis and lipolysis in patients with chronic obstructive pulmonary disease

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Schiffelers, S. L. H., E. E. Blaak, E. M. Baarends, M. A. van Baak, W. H. M. Saris, E. F. M. Wouters, and A. M. W. J. Schols. β -Adrenoceptor-mediated thermogenesis and lipolysis in patients with chronic obstructive pulmonary disease. *Am J Physiol Endocrinol Metab* 280: E357–E364, 2001.—The present study investigated whether development or maintenance of a relatively increased fat mass in normal-weight patients with chronic obstructive pulmonary disease (COPD), despite periods of weight loss, may be related to impaired β -adrenoceptor-mediated responses in lipid utilization and thermogenesis. Nine COPD patients and nine healthy controls (body mass index: 23.0 ± 1.3 vs. 23.8 ± 0.6 kg/m², not significant; fat mass: 19.0 ± 2.1 vs. 11.9 ± 1.5 kg, $P < 0.01$) received consecutive 30-min infusions of 6, 12, and 24 ng·kg fat free mass⁻¹·min⁻¹ isoproterenol. During β -adrenergic stimulation, nonesterified fatty acid levels increased significantly less in COPD patients ($P < 0.001$). Respiratory exchange ratio decreased similarly in both groups, indicating a similar change in the rate of lipid to carbohydrate oxidation. Energy expenditure increased similarly in both groups during β -adrenergic stimulation. However, because plasma isoproterenol concentrations were significantly higher in COPD patients, thermogenesis related to isoproterenol concentration was significantly reduced in this group ($P < 0.05$). In conclusion, β -adrenoceptor-mediated lipolysis and thermogenesis are impaired in COPD patients. This may play a role in the development or maintenance of their relatively increased fat mass.

sympathetic nervous system; fat mass; energy expenditure

WEIGHT LOSS COMMONLY OCCURS in patients with chronic obstructive pulmonary disease (COPD), in particular in the emphysematous subtype (12). Different patterns of body compositional changes are observed in these patients. Although normal weight loss merely comprises loss of fat and fat-free mass, COPD patients may show a depletion of fat-free mass despite a relative preservation of fat mass (2, 10). In the latter group, functional capacity characterized by decreased muscle function, exercise capacity, and even health status is more impaired compared with underweight subjects with a normal fat-free mass (28). Furthermore, recent

studies indicate that the relative or absolute increase in fat mass and decrease in fat-free mass in COPD patients might be related to intrinsic deviations in substrate metabolism, such as an impaired lipolytic response during exercise or insulin infusion (17, 19, 20) and an increased fasting protein turnover (11).

A blunted β -adrenergic response might also play a role in the development or maintenance of an increased fat mass (5). During the infusion of isoproterenol (a nonselective β -adrenoceptor agonist), obese men showed an impaired response in lipolysis and lipid oxidation compared with lean men (3), which favors the development or maintenance of their increased fat mass. Furthermore, when very obese men were compared with very lean men, an impaired thermogenic response was found as well (6). After a weight loss period, these parameters remained impaired (5), suggesting that a diminished capacity to utilize fat may be a primary factor leading to the development of obesity rather than a secondary factor as a result of the obese state.

The relatively increased fat mass in normal-weight patients with COPD might also be explained by a primary impaired response to β -adrenergic stimulation but may also be secondary to their disease or its treatment. COPD patients with emphysema have increased plasma norepinephrine levels at rest (14), suggesting an overstimulation of the sympathetic nervous system (SNS) in the basal state, whereas their chronic β_2 -adrenoceptor agonist use for bronchodilation causes downregulation of SNS responsiveness (33, 43). Furthermore, several studies showed a decreased oxidative capacity in peripheral skeletal muscle that could blunt lipid utilization and thermogenesis (18, 25).

The aim of the present study was to investigate whether development or maintenance of a relatively increased fat mass in normal-weight patients with COPD, despite periods of weight loss, is related to an impaired response in lipid utilization and thermogenesis induced by β -adrenergic stimulation with isoproterenol.

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SUBJECTS AND METHODS

Subjects. Nine male COPD patients with moderate to severe emphysema and nine healthy male age-matched control subjects participated in this study. COPD was diagnosed according to the criteria of the American Thoracic Society (1), and macroscopic emphysema was diagnosed by high-resolution computed tomography. All patients were in clinically stable condition and were weight stable for ≥ 3 mo. However, on average they had lost 3–4 kg body wt in the year preceding the experiment. Patients used inhaled β_2 -sympathomimetics and inhaled corticosteroids. In the 24 h preceding the study, patients were not allowed to use any sympathomimetic drugs to prevent any acute effect of these drugs on energy metabolism. Control subjects were in good health as assessed by medical history and physical examination, and none used β_2 -sympathomimetic drugs. Data on whole body thermogenesis of the control group have been published previously (21). Both patients and controls spent no more than 2 h/wk in organized sports activities; none of the subjects had a history of hypertension, cardiovascular disease, or heart failure. Patients were all ex-smokers, and controls were non-smokers. The study protocol was reviewed and approved by the Ethics Committee of Maastricht University, and all subjects gave informed consent before participating in the study.

Experimental design. Subjects were studied in the morning after an overnight fast. They came to the laboratory by car or by bus to minimize the amount of physical activity before the test. On arrival, a cannula was inserted into a forearm vein of each arm. One cannula was used for the infusion of drugs and the other cannula for the sampling of blood. All measurements were done with the subject in supine position, and room temperature was kept at 21–23°C. The study protocol consisted of four study periods. After a 30-min baseline measurement, subjects received consecutive infusions of 6, 12, and 24 ng·kg fat-free mass (FFM) $^{-1}$ ·min $^{-1}$ isoproterenol (Isoprenaline sulfate, Fresenius, 's Hertogenbosch, The Netherlands), each dose for 30 min. At the end of each 30-min period, a blood sample was taken.

Clinical methods. Body composition of COPD patients was measured by single frequency (50 kHz) bioelectrical impedance analysis (Xitron Technologies, San Diego, CA) with the subject in supine position. FFM was calculated according to the equation of Schols et al. (36), validated for this group of patients. Body density of the control group was determined by hydrostatic weighing with simultaneous lung volume measurement (Volugraph 2000, Mijnhardt, Bunnik, The Netherlands), and body composition was calculated according to the equation of Siri (38).

In patients with COPD, lung function was measured before the isoproterenol infusion test. Forced expiratory volume in 1 s (FEV₁) and inspiratory vital capacity (IVC) were calculated from the flow-volume curve by use of a spirometer (Jaeger, Hoechberg, Germany). Lung function was expressed as percentage of reference value (29).

Whole body energy expenditure and respiratory exchange ratio (RER) were measured by an open-circuit ventilated hood system (Oxycon beta, Mijnhardt, Bunnik, The Netherlands). The airflow rate and the O₂ and CO₂ concentrations of the in- and outflowing air were used to compute O₂ consumption and CO₂ production on-line through an automatic acquisition system connected to a personal computer. Energy expenditure was calculated according to the formula proposed by Weir (42). Energy expenditure and RER values were averaged over the last 10 min of each 30-min period during which steady state occurred.

Heart rate was monitored continuously by conventional electrocardiography, and the mean value over the last 10 min of each 30-min period was used for further analysis.

Analytical methods. Blood samples for the determination of nonesterified fatty acids (NEFA), glucose, and insulin were preserved in sodium-EDTA and those for isoproterenol, norepinephrine, and epinephrine determination were preserved in heparin plus glutathione (1.5% wt/vol). Blood samples were immediately centrifuged for 10 min at 800 g at 4°C. Plasma was transferred into microtest tubes, rapidly frozen in liquid nitrogen, and stored at –70°C until further analysis. Plasma NEFA concentration was measured with the NEFA C kit (99475409, WAKO, Neuss, Germany), and plasma glucose concentration was measured with a glucose kit (Unimate 5, 0736724, Roche Diagnostica, Basel, Switzerland), both on a Cobas-Fara centrifugal analyzer (Roche Diagnostica). Plasma insulin concentration was determined with a double antibody radioimmunoassay (Insulin RIA 100, Pharmacia, Uppsala, Sweden). Plasma isoproterenol, norepinephrine, and epinephrine levels were determined by high-performance liquid chromatography according to the method of Smedes et al. (39). Standard samples with known concentrations were included in each run for quality control.

Data analysis. All data are presented as means \pm SE. Data for energy expenditure were adjusted for FFM for group comparison using linear regression analysis (30).

To summarize the response of each subject to isoproterenol infusion in a single value, β -adrenergically mediated thermogenesis was expressed as the dose and the plasma concentration of isoproterenol required to increase baseline energy expenditure by 15% (dose _{Δ EE=15%} and conc _{Δ EE=15%}, respectively) (6). To evaluate the β -adrenergically-mediated heart rate response, both the chronotropic dose (CD25) and the chronotropic concentration (CC25) were calculated from the dose and plasma concentration of isoproterenol required to increase basal heart rate by 25 beats/min (26). These values were determined by applying individual linear regression analysis to the measured response vs. the dose or plasma concentration of isoproterenol.

The effect of β -adrenergic stimulation between groups was analyzed with two-way repeated-measures ANOVA. Post hoc testing between groups was done with an unpaired *t*-test. The effect of β -adrenergic stimulation within a group was analyzed with one-way repeated-measures ANOVA. A *P* value < 0.05 was regarded as statistically significant.

RESULTS

Physical characteristics of the subjects are given in Table 1. Body weight and body mass index were similar in the two groups. Although patients with COPD had lost 3–4 kg body wt in the year preceding the experiment, they had a significantly higher fat mass ($P < 0.01$) and a significantly lower FFM ($P < 0.05$) compared with control subjects.

Plasma isoproterenol concentrations significantly increased during isoproterenol infusion in COPD patients and control subjects but were significantly higher in the patient group (Fig. 1). At baseline, plasma norepinephrine levels were significantly higher ($P < 0.05$) and plasma epinephrine levels were slightly lower ($P = 0.06$) in patients compared with controls. During β -adrenergic stimulation with isoproterenol, norepinephrine concentrations significantly increased and epinephrine concentrations significantly decreased in both groups. The changes in norepinephrine

Table 1. *Physical characteristics of COPD patients and control subjects*

Parameter	COPD	Control
Body weight, kg	71.7(39.0–88.9)	73.5(66.5–85.9)
Height, m	1.76(1.58–1.93)	1.76(1.68–1.88)
Body mass index, kg/m ²	23.0(15.6–29.2)	23.8(21.6–27.5)
Fat mass, kg	19.0(6.4–30.2)**	11.9(6.3–19.9)
FFM, kg	52.7(32.6–66.5)*	61.6(53.6–71.8)
Age, yr	55(49–62)	51(41–58)
FEV ₁ , % predicted	36(16–65)	
IVC, % predicted	84(33–150)	

Values are means (range) for 9 chronic obstructive pulmonary disease (COPD) patients and 9 control subjects. FFM, fat-free mass; FEV₁, forced expiratory volume in 1 s; IVC, inspiratory vital capacity. Unpaired *t*-test, COPD vs. control: **P* < 0.05, ***P* < 0.01.

and epinephrine levels were comparable between groups (Fig. 1).

At baseline, plasma NEFA concentrations were similar in patients and controls (Fig. 2). However, the increase in plasma NEFA concentration was significantly reduced (*P* < 0.001) in patients with COPD despite the greater increase in plasma isoproterenol concentration, suggesting a blunted β-adrenergically mediated lipolytic response. Plasma glucose and insulin levels were similar in both groups at baseline. Glucose and insulin levels significantly increased during β-adrenergic stimulation, but these increases were not significantly different between groups (Table 2).

Baseline energy expenditure was slightly lower in patients with COPD compared with controls (4.71 ± 0.24 vs. 5.21 ± 0.22 kJ/min, *P* = 0.14), but after adjustment for FFM, baseline energy expenditure was similar in both groups (Fig. 2). During β-adrenergic stimulation, energy expenditure significantly increased in both groups. There was no significant difference in the increase in energy expenditure between COPD patients and control subjects. In addition, dose_{ΔEE=15%} was not different between groups (Table 3). However, when responses were related to plasma isoproterenol concentrations, conc_{ΔEE=15%} was significantly higher (*P* < 0.05) in patients compared with controls, indicating a blunted β-adrenergically mediated thermogenic response in patients with COPD (Fig. 3 and Table 3). RER was similar in both groups at baseline and significantly decreased with isoproterenol, indicating a similar change in the rate of lipid to carbohydrate oxidation during β-adrenergic stimulation (Table 2).

Heart rate was comparable in patients and controls at baseline and similarly increased during β-adrenergic stimulation (Fig. 2). Thus CD25 was not significantly different between groups. When heart rate responses were related to plasma isoproterenol concentrations, CC25 was slightly higher in patients with COPD, but this difference did not reach statistical significance (*P* = 0.11; Fig. 3 and Table 3).

DISCUSSION

The present study intended to investigate whether development or maintenance of a relatively increased

fat mass in normal-weight patients with COPD, despite periods of weight loss, is related to a blunted increase in lipid utilization and thermogenesis during β-adrenergic stimulation with isoproterenol. It was found that the β-adrenoceptor-mediated increase in NEFA concentration was impaired in COPD patients,

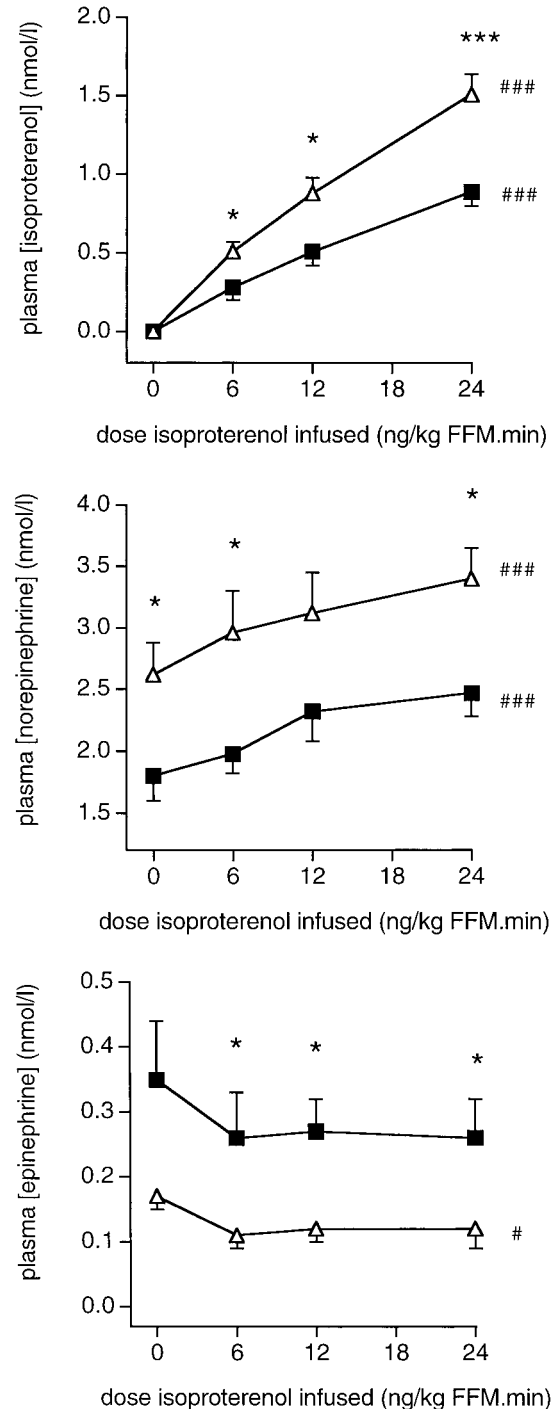


Fig. 1. Plasma isoproterenol, norepinephrine, and epinephrine concentrations during β-adrenergic stimulation with isoproterenol. FFM, fat-free mass. Values are means ± SE for 9 chronic obstructive pulmonary disease (COPD) patients (Δ) and 9 healthy controls (■). One-way repeated-measures ANOVA: **P* < 0.05, ****P* < 0.001; unpaired *t*-test, COPD vs. control: **P* < 0.05, ****P* < 0.001.

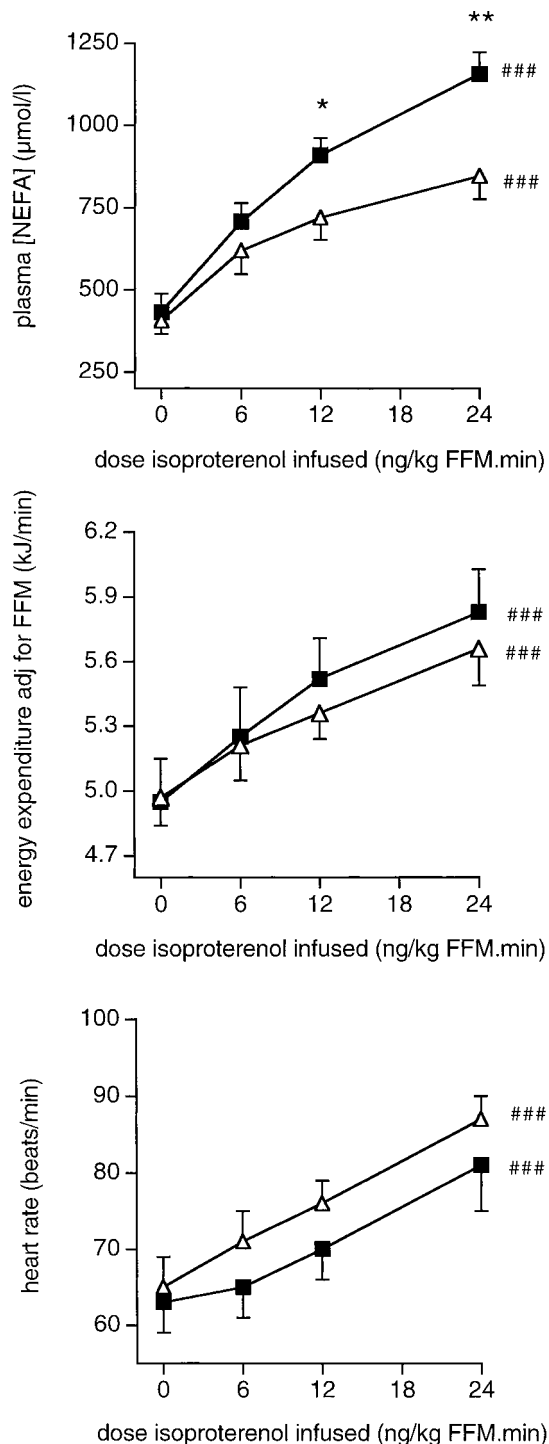


Fig. 2. Plasma nonesterified fatty acid (NEFA) concentration, energy expenditure adjusted for FFM, and heart rate expressed per dose of isoproterenol infused. Values are means \pm SE for 9 COPD patients (Δ) and 9 healthy controls (\blacksquare). One-way repeated-measures ANOVA: ### $P < 0.001$; unpaired t -test, COPD vs. control: * $P < 0.05$, ** $P < 0.01$.

indicating a blunted lipolytic response. RER decreased similarly in both groups, suggesting a similar change in the rate of lipid to carbohydrate oxidation. β -Adrenoceptor-mediated thermogenesis was impaired when related to plasma isoproterenol concentrations. The

impaired release of NEFA from adipose tissue and the reduced thermogenic response may play a role in the development or maintenance of relatively increased fat stores in patients with COPD, even when they lost weight.

COPD patients and control subjects showed a similar response in energy expenditure when related to the dose of isoproterenol infused. However, patients with COPD had significantly higher plasma isoproterenol concentrations and thus an impaired thermogenic response when related to plasma isoproterenol concentration. The heart rate response was also slightly lower in patients with COPD when related to plasma isoproterenol concentration, but this did not reach statistical significance. The differences in plasma isoproterenol concentrations indicate that the pharmacokinetics of isoproterenol are different in patients compared with healthy controls. The reason for this is not clear. Differences in hepatic or renal clearance are not evident, since none of the patients or control subjects were diagnosed with impaired liver or renal function. Another explanation might be a reduction in the number of β -adrenoceptor binding sites. The literature shows that a reduced β -adrenoceptor number on fat cells might be a primary factor leading to the development or maintenance of a relatively increased fat mass (32). On the other hand, chronic β_2 -adrenoceptor agonist administration is also found to reduce the number of β -adrenoceptors on lymphocytes. Fourteen days of oral terbutaline administration is known to reduce the lymphocyte β -adrenoceptor number by $>50\%$ in both normal subjects and asthmatic patients (13, 40, 41). If the β -adrenoceptor number is reduced in these and other tissues and a similar dose of isoproterenol is given to patients and controls, less isoproterenol can bind to the available receptors in patients, and as a consequence, the concentration of free isoproterenol is increased in the patient group. Furthermore, the significantly higher plasma isoproterenol concentrations in the patient group make it clear that individual plasma concentration-response curves instead of dose-response curves should be used in the analysis of these kinds of experiments, because plasma concentration-response curves increase the precision of these infusion tests. This has already been emphasized by others (6, 21, 26).

To our knowledge, this is the first study to report a blunted isoproterenol-induced increase in plasma NEFA concentration in COPD patients. However, the impaired NEFA release might be explained by a decreased lipolytic response and/or increased reesterification within adipose tissue or other tissues. An impaired isoproterenol-induced lipolytic response has been reported before in obese subjects, both in vivo (3) and in vitro (31), indicating that this might be an important explanation for the blunted increase in NEFA concentration in COPD patients with a relatively increased fat mass.

This is also the first study to report an impaired thermogenic response in COPD patients with moderate to severe emphysema. Only Creutzberg et al. (9) did a comparable study in which they measured the acute

Table 2. Measured parameters at baseline and during isoproterenol infusion in COPD patients and control subjects

Parameter	Group	Baseline	Isoproterenol, ng·kg FFM ⁻¹ ·min ⁻¹			ANOVA	
			6	12	24	Treatment	Treatment group
RER	COPD	0.82 ± 0.01	0.83 ± 0.01	0.82 ± 0.01	0.81 ± 0.01	<i>P</i> < 0.01	NS
	Control	0.82 ± 0.01	0.84 ± 0.01	0.81 ± 0.01	0.81 ± 0.01		
Glucose, mmol/l	COPD	5.24 ± 0.21	5.16 ± 0.19	5.12 ± 0.19	5.33 ± 0.18	<i>P</i> < 0.05	NS
	Control	5.00 ± 0.16	5.01 ± 0.12	5.03 ± 0.10	5.22 ± 0.08		
Insulin, mU/l	COPD	5.09 ± 0.45	6.63 ± 0.56	7.26 ± 0.71	8.52 ± 0.96	<i>P</i> < 0.001	NS
	Control	5.86 ± 0.97	6.51 ± 0.50	7.22 ± 0.81	9.30 ± 1.40		

Values are mean ± SE for 9 COPD patients and 9 control subjects. RER, respiratory exchange ratio.

thermogenic effect after salbutamol nebulation. They found no difference in thermogenesis between patients with COPD and age-matched healthy control subjects. However, plasma salbutamol levels were not measured in this experiment, so a possibly reduced thermogenic response related to plasma salbutamol concentrations could not be demonstrated. Furthermore, a reduced isoproterenol-induced increase in thermogenesis has been reported in obese subjects (6). This blunted response might be explained by the impaired lipolytic response, which leads to a reduced NEFA availability in the blood. Therefore, less NEFA can be taken up and oxidized by skeletal muscle, and as a consequence, thermogenesis may be reduced. This hypothesis is supported by another study from our group (34), in which lipolysis was pharmacologically inhibited with acipimox. Concomitant β₁-adrenergic stimulation resulted in a reduced increase in lipolysis and thermogenesis compared with β₁-adrenergic stimulation alone. Furthermore, reduced oxidative capacities in peripheral skeletal muscle, reported both in obesity (7, 37) and in COPD (18, 25), might blunt lipid oxidation and thermogenesis.

The blunted β-adrenoceptor-mediated lipolytic and thermogenic response in patients with COPD might be a primary factor leading to the development of their relatively increased fat stores. This might be caused by an already developed impairment in β-adrenoceptor-

mediated processes before the onset of the disease, as is the case in obesity. In vitro studies in fat cells from obese subjects suggest that the impaired lipolytic response to isoproterenol is due to a significant reduction in cell surface density of the β₂-adrenoceptor (23, 32). In an in vivo study (35), we showed that β₂-adrenoceptor-mediated thermogenesis and lipid utilization are blunted in obese compared with lean subjects, whereas β₁-adrenoceptor-mediated responses are similar in the groups.

The blunted β-adrenergic response might also be secondary to the already developed increased fat stores. Because abdominal subcutaneous adipose tissue blood flow is reduced in obesity (4), fat cell lipolysis might not be fully stimulated, leading to a reduced release of NEFA. Furthermore, due to a possibly reduced abdominal blood flow, which is seen in obese subjects (4), only part of the available NEFA in the interstitial fluid might be taken up into the bloodstream, and the remaining part has to be stored again. These factors might contribute to the maintenance of relatively increased adipose tissue stores.

Regression analysis showed that there was a significant relationship between percent body fat and the increase in plasma NEFA concentration (*r* = -0.56, *P* < 0.02) and percent body fat and the increase in plasma isoproterenol concentration (*r* = 0.47, *P* < 0.05) for the whole group. After reanalysis per subgroup (patients or controls), these significant relationships disappeared, probably due to the small number of subjects. Regression analysis between other combinations of variables, like increase in plasma NEFA concentration, increase in plasma isoproterenol concentration, baseline norepinephrine concentration, and percent body fat revealed no further significant relationships, either in the whole group or in one of the subgroups. Whether the impaired β-adrenergic response in patients with COPD is a cause or a consequence of their increased fat mass needs to be further explored.

Another explanation for the blunted β-adrenergic response during isoproterenol infusion in patients with COPD might be desensitization of the SNS due to the disease. COPD patients are found to have increased plasma norepinephrine levels and decreased plasma epinephrine levels at rest (14). This suggests that sympathetic nerve activity is increased in the basal state.

Table 3. Energy expenditure and heart rate and their sensitivity to β-adrenergic stimulation with isoproterenol in COPD patients and controls

Parameter	COPD	Control
Baseline energy expenditure adjusted for FFM, kJ/min	4.97 ± 0.13	4.95 ± 0.20
Dose _{ΔEE = 15%} , ng·kg FFM ⁻¹ ·min ⁻¹	27 ± 6	22 ± 5
Conc _{ΔEE = 15%} , nmol/l	1.80 ± 0.32*	0.85 ± 0.23
Basal heart rate, beats/min	65 ± 4	63 ± 4
CD25, ng·kg FFM ⁻¹ ·min ⁻¹	23 ± 5	24 ± 3
CC25, nmol/l	1.43 ± 0.25	0.93 ± 0.16

Values are means ± SE for 9 COPD patients and 9 control subjects. Dose_{ΔEE = 15%} and conc_{ΔEE = 15%}, dose or plasma concentration of isoproterenol needed to increase thermogenesis by 15%; CD25 and CC25, dose or plasma concentration of isoproterenol needed to increase heart rate by 25 beats/min. Unpaired *t*-test, COPD vs. control: **P* < 0.05.

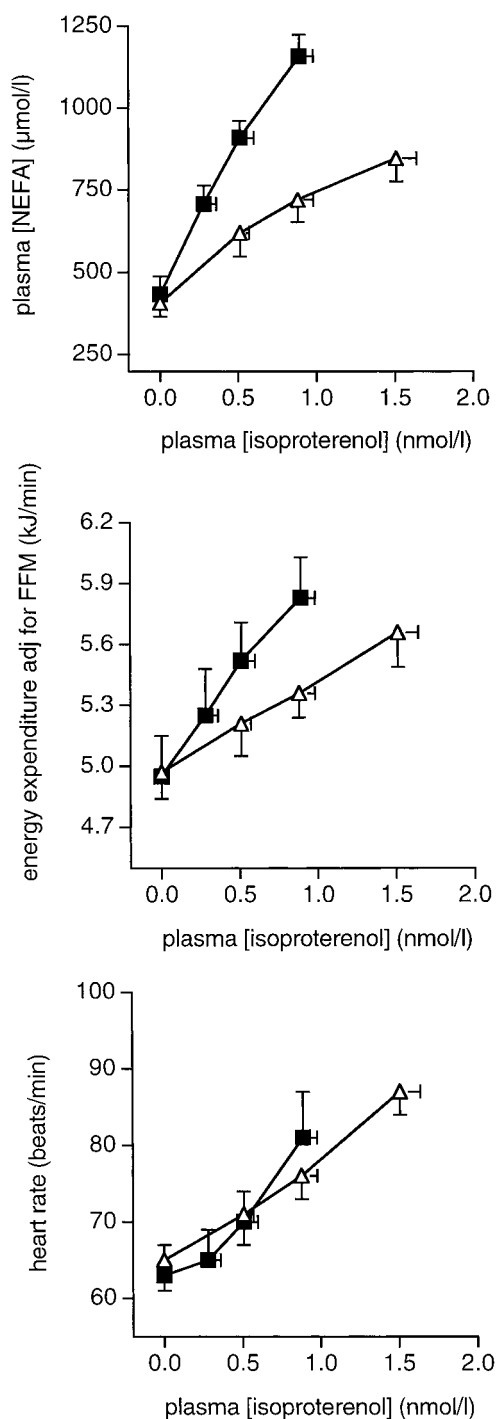


Fig. 3. Plasma NEFA concentration, energy expenditure adjusted for FFM, and heart rate expressed per plasma isoproterenol concentration. Values are means \pm SE for 9 COPD patients (Δ) and 9 healthy controls (\blacksquare).

Because of this chronic overstimulation of the SNS, β -adrenoceptors may become desensitized, and consequently, the response to additional β -adrenergic stimulation might be blunted.

Finally, the impaired SNS response might be related to chronic usage of β_2 -adrenoceptor agonists for bronchodilation. In normal subjects, 2 wk of regular salbu-

tamol inhalation induced a blunted increase in plasma NEFA and glycerol concentrations during salbutamol infusion (15). Thirteen days of salbutamol inhalation (43) or 2 wk of oral terbutaline administration (33) induced impaired thermogenic responses after salbutamol inhalation or isoproterenol infusion, respectively. In COPD patients, the effect of chronic β_2 -adrenoceptor agonist usage on thermogenesis and lipid utilization has never been studied. However, in patients with moderate (22) to severe (27) asthma, who also use β_2 -adrenergic bronchodilators, a blunted increase in plasma NEFA concentration was found during epinephrine infusion. Furthermore, in asthmatic patients using large dosages of β -adrenergic bronchodilators, lymphocyte cAMP production during isoproterenol incubation was significantly reduced compared with that in control subjects (8, 40, 41) or in asthmatic patients on nonadrenergic drugs (8). Moreover, when the asthmatic patients changed to nonadrenergic drugs (8) or a placebo (41), their cAMP response to isoproterenol returned to normal. Furthermore, Makino et al. (24) showed that lymphocyte cAMP production was impaired in asthmatic patients only during incubation with salbutamol and not with norepinephrine ($\beta_1 > \beta_2$ -adrenoceptor affinity) compared with healthy controls. This suggests that chronic β_2 -adrenoceptor agonist administration desensitizes only β_2 -adrenoceptors and not β_1 -adrenoceptors.

In our study, patients were asked to stop using their β_2 -adrenergic bronchodilators 24 h before the start of the experiment to prevent any acute interference with our isoprenaline infusion test. All patients used inhaled salbutamol [plasma half-time ($t_{1/2}$) = 4–6 h] or inhaled salmeterol (plasma $t_{1/2}$ unknown due to very low plasma concentrations after inhalation) for bronchodilation. Considering 24-h withdrawal, plasma salbutamol concentrations would be $<5\%$ of that directly after inhalation and therefore will not directly influence our study. However, the desensitizing effect of chronic β_2 -adrenoceptor agonist usage on the measured parameters is still present after 24-h withdrawal.

Our COPD patients also chronically inhaled corticosteroids, which are known to potentiate the effect of β -adrenergic stimulation. Hui et al. (16) showed that the reduction in lymphocyte β -adrenoceptor number induced by 3–5 wk of oral terbutaline administration was completely reversed 16 h after a single intravenous dose of methylprednisolone in both normal subjects and asthmatic patients. Furthermore, Reynisdottir et al. (31) showed that lipolytic sensitivity to isoproterenol in isolated abdominal adipocytes from asthmatic patients (who only sporadically needed inhaled β_2 -adrenoceptor agonists) increased 50-fold after 7 days of oral prednisolone treatment. Sensitivity to terbutaline increased 25-fold, whereas sensitivity to dobutamine (β_1 -adrenoceptor agonist) remained unchanged after treatment. Furthermore, the number of β_2 -adrenoceptor binding sites increased by 60% after glucocorticosteroid treatment, whereas β_1 -adrenoceptor binding sites were not affected. This suggests that

glucocorticosteroids selectively increase β_2 -adrenoceptor density and function and may possibly reverse the desensitizing effect of chronic β_2 -adrenoceptor agonist usage.

In conclusion, β -adrenoceptor-mediated lipolysis and thermogenesis are reduced in normal-weight patients with COPD with a relatively increased fat mass compared with healthy age-matched control subjects. The impaired release of NEFA from adipose tissue and the reduced thermogenic response may play a role in the development or maintenance of the relatively increased fat stores in these patients, despite periods of weight loss.

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